REMARKS

Reconsideration is requested.

Claims 3, 4, 7, 11-14, 17, 18 and 21-23 have been canceled. New claims 24-30 have been added. The new claims 24-30 are similar to claims 1, 5, 6, 8, 10, 15 and 16 wherein the hemoprotein is specifically defined as hemoglobin. The new claims read on the elected subject matter. The present Amendment does not add claims without canceling a corresponding number of claims. The Amendment does not require further search and/or consideration as the pending claims have been examined at least to the extent the hemoprotein is hemoglobin. See page 2 of the Office Action dated December 15, 2006. No new matter has been added.

Claims 1, 2 and 5-20 are pending. Claims 1, 2, 5, 6, 8, 9, 10, 15, 16, 19, 20 and 24-30 will be pending upon entry of the present Amendment.

To the extent not obviated by the above amendments, the Section 103 rejection of claims 1, 2, 5, 6, 8-10, 15, 16, 19 and 20 over Chauvierre (U.S. Patent Application Publication No. 2004/0028635), Kabanov (U.S. Patent No. 6,333,051), Schmidt (U.S. Patent No. 4,698,387), and Desai (U.S. Patent No. 6,096,331) is traversed. Reconsideration and withdrawal of the rejection are requested in view of the above and the following distinguishing comments.

The deficiencies of the combined teachings of Chauvierre, Schmidt and Desai are of record. See for example, the remarks of Amendment filed September 8, 2009. The additional teachings of Kabanov fail to cure the deficiencies of the combination of

Chauvierre, Schmidt and Desai. Consideration of the following in this regard is requested.

The claimed invention requires a particle, with a specific structure, wherein the core of the particle is specifically defined and the surface of the particle is specifically defined. Schmidt fails to teach a particle of the claimed invention. The polysaccharide "macromolecular agent" of Schmidt would not be on the surface of the any particle alleged to be formed by Schmidt. Schmidt teaches a structure whereby an "adduct" is non-covalently bound to hemoglobin. The "adduct" is formed from a "macromolecular agent". The "anionic ligand" of Schmidt's "adduct" is non-covalently bound to hemoglobin. Schmidt therefore fails to teach or suggest a particle structure of the claims wherein hemoglobin is non-covalently associated to a surface of a particle wherein the surface of the particle consists essentially of a polysaccharide or oligosaccharide. Any particle formed by Schmidt or suggested by Schmidt would presumably not have a surface portion required by the structure of the presently claimed invention.

The combination of cited art would not have made the claimed invention obvious.

The Examiner's confirmation that Desai et al do not disclose that hemoglobin may be present in the polymeric shell of a heparin-coated particle, thereby providing a blood substitute, is again acknowledged[1].

[1] See Advisory Action dated November 23, 2007 and page 10 of the Office Action dated June 23, 2008 ("Desai et al taught the synthesis of nanoparticles comprising synthetic block copolymers (column 10, lines 3-22), attached to biocompatible materials, i.e. polysaccharides (column 9, lines 42-49). Desai et al do not explicitly disclose heparin as a contemplated polysaccharide; however, absent evidence to the contrary, the art recognizes that heparin is a polysaccharide. Desai et al also contemplate that

One of ordinary skill in the art will understand that compounds may associate non-covalently, as opposed to, for example, covalent attachments or associations. The distinction is important and significant in view of the art relied upon by the Examiner. Specifically, the cited Desai patent fails to describe "the ultrasonic irradiation process described above" or further describe how hemoglobin is to "participate in the delivery of a biologic".

The cited Desai patent however is a continuation-in-part of U.S. Patent No. 5,916,596, which is a continuation-in-part of U.S. Patent No. 5,665,382. Each of the parent patents are incorporated-by-reference in the cited Desai patent.

U.S. Patent No. 5,665,382, (herein after Grinstaff) describes and claims methods of preparing pharmaceutically active agents for in vivo delivery. The claimed method of Grinstaff involves cross-linking disulfide bonds of a biocompatible material with high intensity ultrasound to form a polymeric shell of the crosslinked material which contains a pharmaceutically active agent in the polymeric shell. See claim 1 of Grinstaff for example.[2] The cross-linking reaction of Grinstaff, and by incorporation Desai, is a covalent attachment which is distinct from and would have made obvious the non-covalent association of the presently claimed invention.

Claim 4 of Grinstaff specifically includes hemoglobin as a protein biocompatible material containing cross-linkable disulfide bonds which may be used to form a

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hemoglobin would be present in the polymeric shell (column 9, line 54; column 11, line 63), thereby providing a blood substitute.")

[2] The fact that the presently claimed invention allows for inclusion of active material in the recited particle does not suggest that it would have been obvious from the art to have associated a hemoprotein non-covalently with the surface portion of the particle as appears to be asserted by the Examiner. See pages 9 and 10, for example, of the Office Action dated June 23, 2008.

polymeric shell of Grinstaff. Claim 3 of Grinstaff alternatively states that "polysaccharides containing sulfhydryl groups and/or disulfide groups" may be biocompatible materials which may be used to form a polymeric shell of Grinstaff.

The cited Desai patent therefore, in referring to hemoglobin in the passages of column 11 of the Desai patent reproduced in the applicants previous Remarks, will be understood by one of ordinary skill in the art to be a reference to a polymeric shell formed of cross-linked hemoglobin. Alternatively, the cited Desai patent will be understood, from the whole of the patent and its incorporated-by-reference parent patent (i.e., Grinstaff), to relate to a polymeric shell formed of cross-linked polysaccharides containing disulfide or sulfhydryl groups.

Schmidt teaches that cross-linked hemoglobin is not ideally suited for physiological uses. See columns 1 and 2 of Schmidt.

Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked hemoglobin "coated with" (see Advisory Action dated November 23, 2007) or associated with heparin or any other saccharide or polysaccharide. Neither Desai nor Grinstaff teach or suggest a polymeric shell formed of cross-linked polysaccharides containing sulfhydryl groups associated with a protein, such as hemoglobin. The Examiner will appreciate that heparin is not a saccharide or polysaccharide containing sulfhydryl or disulfide groups[3], as would be required according to the teachings of Grinstaff and Desai to form a polymeric shell with high intensity ultrasound.

[3] Heparin is a mucopolysaccharide with a molecular weight ranging from 6,000 to 40,000 Da. The average molecular of most commercial heparin preparations is in the range of 12,000 - 15,000. The polymeric chain is composed of repeating disaccharide unit of D-glucosamine and uronic acid linked by 1->4 interglycosidic bond. The uronic acid residue could be either D-glucuronic acid or L-iduronic acid.

Moreover, Grinstaff further describes the aim and purpose of Desai's brief mention of hemoglobin polymeric shells in the passage from column 19, line 22 through column 21, line 4 of Grinstaff reproduced in the Remarks of the applicants previous submission, which will be understood by one of ordinary skill in the art to clarify the vague reference in Desai to the use of hemoglobin polymeric shells as specific targeting or delivery agents. Specifically, Desai lists "physiologically active gasses", among the following broad genus of "biologic[s]" which may be delivered by the particles of polymeric shells (see column 9, lines 17-27 of Desai (as obtained from www.uspto.gov):

> As used herein, the term "biologic" refers to pharmaceutically active agents (such as analgesic agents, anesthetic agents, anti-asthamatic agents, antibiotics, anti-depressant agents, anti-diabetic agents, anti-fungal agents, anti-hypertensive agents, anti-inflammatory agents, anti-neoplastic agents, anxiolytic agents, enzymatically active agents, nucleic acid constructs, immunostimulating agents, immunosuppressive agents, physiologically active gases, vaccines, and the like), diagnostic agents (such as ultrasound contrast agents, radiocontrast agents, or magnetic contrast agents), agents of nutritional value, and the like.

The description in Grinstaff to the use of particles of hemoglobin crosslinked polymeric shells containing oxygen to deliver oxygen is consistent with, and further

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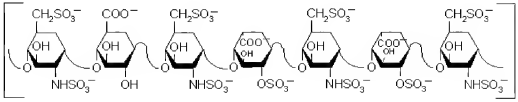
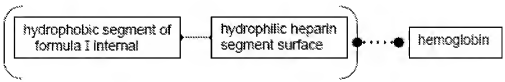
(Structure below) Few hydroxyl groups on each of these monosaccharide residues may be sulfated giving rise to a polymer with that is highly negatively charged. The average negative charge of individual saccharide residues is about 2.3.



explains, the aim and intent and teaching of Desai in the only two instances where hemoglobin is mentioned as a crosslinkable material of the polymeric shell of Desai's particles.

The Examiner is again urged to appreciate that the presently claimed invention provides a product of nanoparticles which include a sequenced block polymer with a particle core consisting essentially of the hydrophobic segment of formula (I), and a heparin saccharide hydrophilic segment, for example, at the surface of the particle, which is in turn associated with hemoglobin at the surface of the particle. This structure may be simply illustrated, without limitations, as the following linear representation of a component of the claimed nanoparticles, wherein the structure in brackets forms the nanoparticles and the hemoglobin is associated with the surface which contains the hydrophilic heparin:



In contrast to the above non-limiting schematic of an embodiment of the presently claimed invention, Desai teaches a particle shell of preferably crosslinked albumin or other disulfide or sulfhydryl containing proteins, such as hemoglobin (as further elucidated by Grinstaff which is incorporated-by-reference in Desai), which may be used as a targeting agent for chemotherapeutic drugs or encapsulated oxygen (in the case of crosslinked hemoglobin polymeric shells). Neither Desai nor Grinstaff teach

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http://www.people.vcu.edu/~urdesai/hep.htm#Heparin%20-%20Structure

or suggest nanoparticles made of polymeric shells containing a combination of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide, such as heparin, in a particle shell, which is non-covalently associated with hemoglobin.

For reasons which are of record, the applicants submit that, in the case of hemoglobin, Desai describes cross-linked hemoglobin as a cross linked particle shell and that it would have been contrary to Desai to have non-covalently associated hemoglobin to a shell of a particle containing a saccharide hydrophilic segment.

Desai, at best, teaches the production of particles of crosslinked albumin, or other disulfide- or sulfhydryl-containing proteins (or disulfide- or sulfhydryl-containing saccharides such as hemoglobin) for delivery of encapsulated chemotherapeutics (or encapsulated oxygen in the case of the crosslinked "megameric" hemoglobin particles of Desai as elucidated by Grinstaff). Desai and Grinstaff teach that nanoparticles of Desai are, in one embodiment, crosslinked hemoglobin as hemoglobin contains cross-linkable sulfhydryl or disulfide groups and can be used not only to administer encapsulated oxygen but can also be used to transport oxygen in vivo as the ultrasonic crosslinking method of Desai/Grinstaff allegedly does not substantially diminish the native oxygen-exchange capacity of the hemoglobin.

The Examiner has appreciated that nanoparticles of a sequenced block polymer of formula (I) of the present claims covalently linked to a saccharide were known in the art.[4] More specifically, the Examiner appreciates that Chauvierre describes

[4] See page 10, ¶ ii) of the Office Action dated June 23, 2008.

nanoparticles of the claims.[5] The present specification further refers to Chauvierre in describing the particles of the present claims.[6]

With respect to the structure of the nanoparticles of the present invention, which the Examiner understands to have been known in the art, Chauvierre teaches that (emphasis added): [7]

> [0039] In the specific case of particles and micelles, it is probable that the copolymer has a structure arranged as follows: the chains of the same nature, that is to say saccharide or hydrophobic chains, group together, either to form the core structure of the micelle or particle or the brush-like ring around this core structure. Their distribution between the core structure and the ring will, of course, depend on the nature, aqueous or organic, of the solvent in which the particles or micelles are dispersed. The term "brush-like ring" is intended to denote a structure in which the segments constituting the ring are bonded via one of their ends to the segments constituting the core. Their free ends constitute the periphery of the ring. Thus, in aqueous medium, the hydrophobic segments are grouped together so as to form the core and the segments of saccharide nature are positioned in a brush-like ring all around this core. In a solvent or organic type, this arrangement between the two types of segment is reversed: the core is of hydrophilic nature and is thus formed of the segments of saccharide nature and the brush-like ring is of hydrophobic nature and is thus formed of the segments of general formula (I).

Moreover, Chauvierre teaches that the brush-like structure of the particles of the present claims are distinguished from, for example, nanoparticles based on amphiphilic block copolymers comprising dextran and poly(alkyl cyanoacrylate) segments derived

[5] See page 5 of the Office Action dated June 23, 2008 ("Chauvierre et al teach the synthesis of nanoparticles of Inm to Imm [0045-46] comprising a core portion and a surface portion forming a sequenced block copolymer, said core portion comprising at least one hydrophobic segment having the formula as taught in Formula I, wherein "X" may be a "CN" moiety, wherein the hydrophobic segment may be a poly(alkylcyanoacrylate) [0010-0019], [0039] [0043-44] conjugated to a saccharide hydrophilic that may be heparin [0028].")

from the anionic polymerization of cyanoacrylate monomers in the presence of dextran, which have grafted structures. Such grafted structures had been previously described by S. J. Douglas et al.; Journal of Controlled Release (1986), 15-23).[8]

The copolymers of the present invention are distinguished from grafted structure of the prior copolymers in that the grafted structures can not contain the brush-like ring structure in an aqueous medium as several hydrophobic segments are covalently bonded to a single chain of saccharide nature.[9] Chauvierre teaches that the block form of the copolymers distinguish the copolymers of the claims and provide the particles of the claims with their definitive structure. More specifically, Chauvierre describes as how the block form of the claimed copolymer is inaccessible by the previously used anionic polymerization.[10] One of ordinary skill in the art will appreciate from, for example, Chauvierre that the block structure of the claimed particles do not include side branches of saccharide nature on the hydrophobic segment or side branches of hydrophobic nature on the segment of saccharide nature, as would be found in a grafted structure.[11]

The claimed structure will be understood to inherently contain the "brush-like" structure, as described by Chauvierre.

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[6] See page 3, lines 20-29 of the present specification.
[7] See reproduction of US 2004/0028635 available at www.uspto.gov.
[8] See ¶[0005] of Chauvierre.
[9] See ¶[0040] of Chauvierre.
[10] See ¶[0006] - [0009] of Chauvierre.
[11] See ¶[0018] of Chauvierre. See also Bertholon et al. "Properties of Polysaccharides Grafted on Nanoparticles Investigated by EPR" Langmuir 2006, 22, 5485-5490; and Bertholon et al. "Characterization of Dextran - Poly(isobutylcyanoacrylate) Copolymers Obtained by Redox Radical and Anionic Emulsion Polymerization" Macromolecules 2006, 39, 3559-3567 (copies submitted herewith).

The non-covalent association of a hemoglobin with a surface portion of the particles of the invention, as claimed, would not have been obvious from the cited combination of art.

It is this "brush-like" structure inherent to the claimed structure that confers to the nanoparticles the long circulating life that is essential for their application as blood substitutes. There was no reasonable or predictable expectation of success from the cited references, or from the general knowledge in the art, that the surface properties of the nanoparticles, in particular their long- circulating life in blood, would not be negatively impacted if they were associated with hemoglobin.

The inventors demonstrated that the binding of hemoglobin to the heparin coated nanoparticles did not affect the spectral properties of the hemoglobin, since the main characteristic peaks of hemoglobin CO were still present. These spectral characteristics together with the fact that the hemoglobin loaded heparin coated nanoparticles turned to the typical red color of hemoglobin after reduction with sodium dithionite and equilibration with CO were good indicators that hemoglobin maintained its capacity to exchange gas. Finally, results of zeta potential and of complement activation performed on the nanoparticles loaded with hemoglobin showed that the association of hemoglobin with the nanoparticle surface did not change the surface properties of the carrier, in terms of their zeta potential and of their complement activation properties, that are

essential to define the fate of the nanoparticles m vivo after intravenous administration.[12]

These results are unexpected in view of, for example, the Desai patent, as elucidated by Grinstaff, which describes the unpredictability of hemoglobin-containing blood substitutes. Specifically, Grinstaff is believed to teach the importance of highly cross-linked hemoglobin polymer particles which is not required by and would be contrary to the presently claimed invention. Schmidt and the newly cited art fail to cure these deficiencies.

Kabanov teaches nanogel particles made of networks of cross-linked polymer fragments wherein the fragments comprise at least one polycation fragment and at least one non-ionic homopolymers or copolymer. The non-ionic polymer fragment may be a polysaccharide. The nanogel particles may be loaded with a variety of biological agents . The biological agents include proteins. Neither hemoproteins nor hemoglobin are specifically described. The nanogels of the cited art are porous materials and the immobilization of the biological agents (such as proteins) in the nanogel networks is in the entire volume of the network rather than on the surface. The teachings of the further reference therefore fail to cure the deficiencies of the remaining recited references.

Further, there was no reasonable or predictable expectation of success that the hydrodynamic radius of the nanoparticles of the claims would not be negatively affected by association of hemoglobin at their surface. The inventors demonstrated that the size

[12] See Chauvierre et al. Cell. Molec. Biol., 2004, 50(3), 233-239 "A New Generation of Polymer

of nanoparticles containing heparin was not significantly affected by the association of hemoglobin.[13] Moreover, there was no reasonable or predictable expectation of success that the associated hemoglobin would retain its capacity of transporting gases such as oxygen or carbon monoxide. The inventors have demonstrated that hemoglobin associated with the particles, as claimed, is functional.

Finally, there was no reasonable or predictable expectation of success that the particles of the invention non-covalently associated with a hemoprotein would not activate complement. In fact, the applicants believe it would have been reasonable to expect that a hemoprotein associated with a surface saccharide of a particle would activate complement. The applicants believe the previously-submitted Andersson et al[14] demonstrates an expectation that the nascent C3b molecule of the complement pathway is able to bind specifically to proteins and carbohydrates via free hydroxyl or amino groups, forming covalent ester or amide bonds, respectively. The applicants believe that one of ordinary skill in the art would have expected that the either or both of the carbohydrates, such as dextran, or hemoglobin of the surface of the particles of the claims would activate complement. The applicants have demonstrated however that particles of the claims do not activate complement.

The claimed invention provides unexpected and surprising advantages which are persuasive evidence that the claimed products would not have been obvious in view of the cited combination of art.

Nanoparticles For Drug Delivery" (of record).

[13] See Chauvierre et al, Biomaterials, 2004, 25, 3081-3086 "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier" (of record).

The applicants request consideration of the following excerpts from several publications which support the fact that it could not be reasonably predicted that non-covalent association of a hemoprotein on the surface of the claimed nanoparticles would not result in loss of functionality of the hemoprotein. The references (a)-(d) below, published after the present application was filed, demonstrate that the claimed invention was not predictable from the cited art.

(a) Jeffrey J Gray ("The interaction of proteins with solid surfaces" Current Opinion in Structural Biology, Volume 14, Issue 1, February 2004, Pages 110-115), is a general publication directed to protein adsorption on solid surfaces wherein the authors describe unfolding of a protein upon being adsorbed on a solid surface

(b) Bellezza Fet al ("Structure, stability, and activity of myoglobin adsorbed onto phosphate-grafted zirconia nanoparticles", Langmuir. 2007 Dec 18;23(26):13007-12. Epub 2007 Nov 17), explores the adsorption of myoglobin and is similar to Gray in its conclusions.

(c) Iafisco M, et al. (2008 May 6;24(9):4924-30. Epub 2008 Mar 29), describes a study of the adsorption of myoglobin on another nanoparticulate surface and conclude that protein adsorption is a complex phenomenon which involves conformational changes. The authors report that myoglobin underwent conformational changes affecting the heme.

(d) The Examiner is further requested to consider the attached Henzler et al. ("Adsorption of Bovine Hemoglobin onto Spherical Polyelectrolyte Brushes Monitored by

[14] Andersson et al "Binding of C3 fragments on top of adsorbed plasma proteins during

Small-Angle X-ray Scattering and Fourier Transform Infrared Spectroscopy", Biomacromolecules, 2007, 8: 3674-3681) which describes the adsorption of hemoglobin on nanoparticles with a brush-like structure. The nanoparticles structure of the publication is similar to that of the claimed nanoparticles: a hydrophobic core, and hydrophilic fragments arranged at the surface of the nanoparticles in a brush-like structure.

In the Henzler publication , the hydrophilic fragment is not an oligosaccharide or polysaccharide. The fragment bears polar $-SO_3^-$ groups, which are also present in the heparin structure.

This article confirms the previously stated observations that there was no reasonable expectation of success in that a hemoprotein adsorbed on a surface would retain its biological activity. The article describes hemoglobin on a surface that bears some similarities with the surface of the claimed nanoparticles. The Examiner is requested to see, for example, Figure 1 of the publication.

The reference describes that accumulation of protein at the core surface indicates either decomposition of the tetramer into subunits or unfolding of the protein induced by adsorption onto the hydrophobic PS core. The reference describes that a comparison of the spectra of the adsorbed hemoglobin with the native protein provides further insight to the conformational changes caused by the interaction with the SPB (Figure 7). The reference describes that the difference in the two protein spectra reveals a significant change in the secondary structure induced by the adsorption. The

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complement activation on a model biomaterial surface" Biomaterials 26 (2005) 1477-1485.

reference describe that the marked structural changes have to be ascribed to the interaction of the BHb with the carrier particles of the reference and that such conformational changes can be induced by the contact to the hydrophobic core and interactions with the hydrophobic backbone of PSS as shown by SAXS experiments. The reference describes that the secondary structure of the adsorbed BHb changes significantly upon adsorption due to hydrophobic interactions. The reference concludes that the uptake of hemoglobin into the brush of the reference leads to a significant loss.

By contrast, the applicants have demonstrated hemoglobin activity is retained with particles of the invention. See Chauvierre et al, Biomaterials, 2004, 25, 3081-3086 "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier" (of record).

The Examiner is also requested to see Andersson et al ("Binding of C3 fragments on top of adsorbed plasma proteins during complement activation on a model biomaterial surface", Biomaterials, Volume 26, Issue 13, May 2005, Pages 1477-1485 (attached)), which describes that complement activation is triggered by OH and NH_2 groups of carbohydrates and proteins, and that proteins were highly suspected to be responsible for this activation. It also demonstrates that a protein adsorbed on a nanoparticle surface can activate the complement system.

The presently claimed nanoparticles have carbohydrates on the nanoparticle surface (e.g., heparin, dextran). Although heparin is known to have anticomplement activation properties, dextran does not. In addition, a protein is adsorbed on the surface of the claimed particles.

Accordingly, in light of the Andersson article and in the absence of the present disclosure, one of ordinary skill in the art may reasonably predict that the nanoparticles would activate the complement system.

The present applicants have discovered, quite unexpectedly however that complement was not activated after adsorption of the hemoglobin. (Chauvierre et al, "A New Generation of Polymer Nanoparticles for Drug Delivery", Cellular and Molecular Biology, 50 (3), pp.233-239, 05/2004 (of record) ; Chauvierre et al, "Novel Polysaccharide-Decorated Poly(Isobutyl Cyanoacrylate) Nanoparticles", Pharmaceutical Research, 20 (11), pp.1786-1793, 2003 (of record)). This property is important in increasing circulation time after administration.

The present invention also unexpectedly provides nanoparticles whose physico-chemical properties are not substantially altered upon non-covalent association with hemoglobin. See Chauvierre et al, "Heparin coated poly(alkylcyanoacrylate) nanoparticles coupled to hemoglobin: a new oxygen carrier", Biomaterials 25 (2004) 3081-3086 (of record) One of the important physico-chemical properties is the hydrodynamic radius of the nanoparticles, which the inventors have discovered to not be significantly altered by non-covalent association of hemoglobin.

Moreover, a cytotoxicity study has revealed that the claimed hemoglobin-associated nanoparticles exhibit a much lower cytotoxicity level than nanoparticles which are not associated with hemoglobin. A comparative study has also showed that the claimed nanoparticles, when non-covalently associated with hemoglobin at their surface, exhibit a much lower cytotoxicity level than nanoparticles of the prior art

similarly non-covalently associated with hemoglobin. The nanoparticles made according to the prior art were prepared by anionic emulsion polymerization (AEP). The nanoparticles of the claimed invention are prepared by redox radical emulsion polymerization (RREP). This polymerization technique leads to nanoparticles having the brush-like arrangement of the hydrophilic fragment, which was extensively discussed in previous remarks of record. This brush-like structure is inherent to the claimed nanoparticle. The results of these studies are reported in Chauvierre et al., International Journal of Pharmaceutics, 338, pp.327-332, 06/2007 (of record).

The claims are submitted to be patentable over the cited combination of art. Withdrawal of the Section 103 rejection is requested.

The claims are submitted to be in condition for allowance and a Notice to that effect is requested. The Examiner is requested to contact the undersigned, preferably by telephone, in the event anything further is required.

Respectfully submitted,

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